

REMARKS

Applicants submit this amendment to insert the correct SEQ ID NOS of the Substitute Sequence Listing filed on June 29, 2000.

Applicants believe the present application is now in condition for allowance.

If the Examiner has any questions concerning this application, he or she is requested to contact the undersigned.

Respectfully submitted,

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By

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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicant(s) hereby petition for any needed extension of time.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

On page 22, delete the first full paragraph:

Once the starting plasmid DNAs containing the desired human FRs were selected, PCR primers were designed to enable the substitution of the mouse PM-1 CDRs in place of the mouse D1.3 CDRs. For each reshaped human PM-1 V region, three primers containing the DNA sequences coding for the mouse PM-1 CDRs and two primers flanking the entire DNA sequence coding for the reshaped human V region were designated and synthesized. Using the five PCR primers in a series of PCR reactions yielded a PCR product that consisted of the human FRs present in the starting reshaped human V region and the CDRs present in mouse PM-1 V region (see Example 7, and Figures 7 and 8). The PCR products were cloned and sequenced to ensure that the entire DNA sequence of version "a" of reshaped human PM-1 L and H chain V region coded for correct amino acid sequence ~~(SEQ ID NO: 63)~~ (SEQ ID NO: 64).

On page 26, delete the second full paragraph:

The DNA and amino acid sequences of the final 20 versions of reshaped human PM-1 L and H chain V regions, as altered to improve expression levels, are shown in ~~SEQ ID NOS: 67 and 65~~ SEQ ID NOS: 67 and 68, and SEQ ID NOS 65 and 66. These DNA sequences code for version "a" of the reshaped human PM-1 L chain V region as shown in Table 2 and version "f" of the reshaped human PM-1 H chain V region as shown in Table 3. When inserted into the HEF-1 α expression vectors (Figure 15), these vectors transiently produce approximately 2 μ g/ml of antibody in transfected cos cells. In order to stably produce larger amounts of reshaped human PM-1 antibody, a new HEF-1 α expression vector incorporating the dhfr gene was constructed (see Example 10, Fig. 11). The "crippled" dhfr gene was introduced into the HEF-1 α vector expressing human gamma-1 H chains as was described for the HCMV vector expressing human gamma-1 H chains. The HEF-1 α vector expressing reshaped, human PM-1 L chains and the HEF-1 α -dhfr vector expressing reshaped human PM-1 H chains were co-transfected into CHO dhfr(-) cells.

On page 36, delete the second full paragraph:

In a preferred embodiment, the L chain CDRs have amino acid sequences shown in any one of SEQ ID NOS: 25, 29, 33 and 37 wherein the stretches of the amino acid sequences are defined in Table 9; the ~~L chain~~ H chain CDRs have amino acid sequences shown in any one of SEQ ID NOS: 27, 31, 35 and 39 wherein the stretches of the amino acid sequences are defined in Table 9; human L chain FRs are derived from the REI; and human H chain FRs are derived from the NEW or HAX.

On page 43, delete Table 8:

Table 8

Plasmid	SEQ. ID NO	Accession No.
p12-k2	24	NCIHB 40367
p12-h2	25 <u>26</u>	NCIMB 40363
pPM-k3	26 <u>28</u>	NCIHB 40366
pPM-h1	27 <u>30</u>	NCIHB 40362
p64-k4	28 <u>32</u>	NCIMB 40368
p64-h2	29 <u>34</u>	NCIHB 40364
p146-k3	30 <u>36</u>	NCIMB 40369
p146-h1	31 <u>38</u>	NCIHB 40365

On page 44, delete Table 9:

Table 9

plasmid	SEQ ID NO	CDR(1)	CDR(2)	CDR(3)
		(Amino acid No.)		
p12-k2	24	24-38	54-60	93-101
p12-h2	25 <u>26</u>	31-35	50-66	99-105
pPM-k3	26 <u>28</u>	24-34	50-56	89-97

pPM-h1	27 <u>30</u>	31-36	51-66	99-108
p64-k4	28 <u>32</u>	24-38	54-60	93-101
p64-h2	29 <u>34</u>	31-35	50-66	99-109
p146-k3	30 <u>36</u>	24-34	50-56	89-97
p146-h1	31 <u>38</u>	31-35	50-66	99-106

On page 65 and bridging page 66, delete the last full paragraph:

RVh-PM1f-4 was constructed by replacing the HindIII-BamHI fragment of RVh-PM1f with the HindIII-BamHI fragment excised from pUC-RVh-PM1f-4. Sequence of reshaped human PM-1 antibody L chain V region version "a" wherein introns have been deleted is shown in ~~SEQ ID NO: 67~~ SEQ ID NOS: 67 and 68, and sequence of reshaped human PM-1 antibody H chain V region version "f" wherein have been deleted is shown in ~~SEQ ID NO: 65~~ SEQ ID NOS: 65 and 66.

On page 68, delete the second full paragraph:

The second PCR product of 558 bp length containing an L chain V region into which CDRs of the mouse monoclonal antibody AUK 12-20 L chain had been grafted was purified by a 2.0% low melting agarose gel, and after digestion with BamHI and HindIII, subcloned into a pUC19 vector to obtain pUC-RL_L-1220a, and sequenced. A resulting amino acid sequence of the L chain V region and a nucleotide sequence encoding the amino acid sequence is shown in ~~SEQ ID NO: 82~~ SEQ ID NOS: 82 and 83.

On page 73, delete the second full paragraph:

Note, an amino acid sequence of the reshaped human AUK 12-20 antibody H chain V region version "b" and a nucleotide sequence coding therefor in the plasmid pUC-RV_H-1220b is shown in ~~SEQ ID NO: 96~~ SEQ ID NOS: 97 and 96; and an amino acid sequence of the reshaped human AUK 12-20 antibody H chain V region version "d" and a nucleotide sequence coding therefor in the plasmid pUC-RV_H-1220d is shown in ~~SEQ ID NO: 98~~ SEQ ID NOS: 99 and 98